Polycythemia

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ABSTRACT

Polycythemia is a disease state in which the red blood cell numbers are increased in the blood (erythrocytosis), which in turn makes blood thicker and can cause circulatory problems. Polycythemia Vera is a stem cell disease belonged to a group of myeloproliferative neoplasm in which the erythroid progenitors are overly proliferated by acquired mutation of the JAK2 gene, resulting in excessive erythrocytosis. Secondary Polycythemia refers erythrocytosis due to underlying conditions. It is usually associated with increased blood erythropoietin levels as a compensatory reaction to tissue hypoxia, which can be seen in patients with chronic lung disease or sleep apnea or living at high altitudes. Certain tumors produce the erythropoietin and testosterone increases the blood erythropoietin level, resulting in secondary polycythemia. Relative polycythemia is the consequence of plasma volume contraction, falsely raising the RBC count and hemoglobin/hematocrit level in CBC. Two cases of polycythemia are presented: 1) a patient with polycythemia vera and 2) a patient with secondary polycythemia. Various types of polycythemia are discussed with an updated review covering the etiology, clinical manifestation, diagnostic approach and treatment.

INTRODUCTION

Polycythemia refers to an increase in erythrocytes (red blood cells: RBCs) in the body. Too many RBCs cause the blood to be thicker, which in turn, increases the risk of various health problems. Polycythemia can have different causes, and each of them has its own treatment options.

The principal function of erythrocyte is the transport of oxygen. Erythropoiesis proceeds at a rate consistent with the demand for oxygen-carrying capacity, and the major regulator of erythrocyte production is erythropoietin (EPO). EPO is produced primarily by the kidney under control of a tissue oxygenation sensor.[1]

Secondary erythrocytosis results from either physiologically appropriate compensation for inadequate tissue oxygenation which can be seen in patients with lung disease or from inappropriate stimulation of erythropoiesis by EPO-producing tumors or by testosterone therapy. Erythrocytosis increases oxygen-carrying capacity of the blood, but at high hematocrit levels increased blood viscosity may result in decreased tissue oxygen delivery.[2,5]

However, if the bone marrow keeps producing RBCs without any reason, it is called Primary Polycythemia or

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Polycythemia Vera (PV). The PV is a trilineage, Philadelphia chromosome–negative myeloproliferative neoplasm (MPN) characterized by chronic, unregulated proliferation of erythrocytes and leukocytes and/or platelets.[2] Although leukocytosis and thrombocytosis frequently accompany, erythrocytosis is the most prominent clinical expression of PV.[2,3] A somatic (non-hereditary) mutation (V617F) in the JAK2 gene is found in almost all cases of PV.[3]

Relative polycythemia is an apparent rise of the erythrocyte level in the blood; however, the underlying cause is reduced blood plasma. Relative polycythemia is often caused by loss of body fluids, such as through burns, dehydration, and stress.[3]

CASE REPORT 1

A 76-year-old Hispanic woman was referred for a hematology consultation with increased hemoglobin and platelet counts. CBC showed:

- WBC 7.9 k/uL
- RBC 6.45 mil/uL
- hemoglobin 16.3 k/uL
- hematocrit 51.5%
- MCV 79.3
- platelet 512 k/uL

She has occasional headaches and mild generalized weakness which she attributes to her old age. She denied chronic cough, dyspnea, chest pain, dizziness, excessive snoring, or pruritus. She has no significant medical history such as lung disease, cancer, stroke or coronary artery disease and her only medication is aspirin 81 mg/day. She doesn't use tobacco or alcohol. The family history is not contributory. The comprehensive metabolic panel was not remarkable. Physical examination showed BP 110/70, pulse oximetry in room air 97%, regular pulse at 63/min, no peripheral lymphadenopathy, clear lung sound and normal heart sound, no hepatosplenomegaly, trace leg edema, and varicose veins in lower legs. She had a red face. The EPO level was abnormally low at 1.6 mIU/mL (normal; 2.6-18.5). Because PV was strongly suspected, JAK2 V617F mutation was ordered, which came back positive. The serum ferritin level was lower-normal at 34 ng/mL. She was diagnosed to have PV, and hydroxyurea was started at 500 mg a day. The hemoglobin, hematocrit and platelet counts were gradually decreased. She felt much more alert and energetic, which were noticed by her daughter. The CBC done 3 months later showed:

- WBC 7.1 k/uL
- hemoglobin 14.3 g/dL
- hematocrit 41.5%
- platelet 391 k/uL

CASE REPORT 2

A 65-year-old white man was referred for a hematology evaluation because of increased hemoglobin and hematocrit at 18.5 g/dL and 54.2 % respectively. The RBC count was 6.17 mil/uL (normal 4.2-5.80), WBC 5.5 k/uL and platelet 243 k/uL. He had no history of chronic lung or heart disease. He was not a smoker. He was taking metoprolol and losartan for hypertension. Because of hypotestosteronemia causing low energy level and libido, he was on testosterone implant therapy.

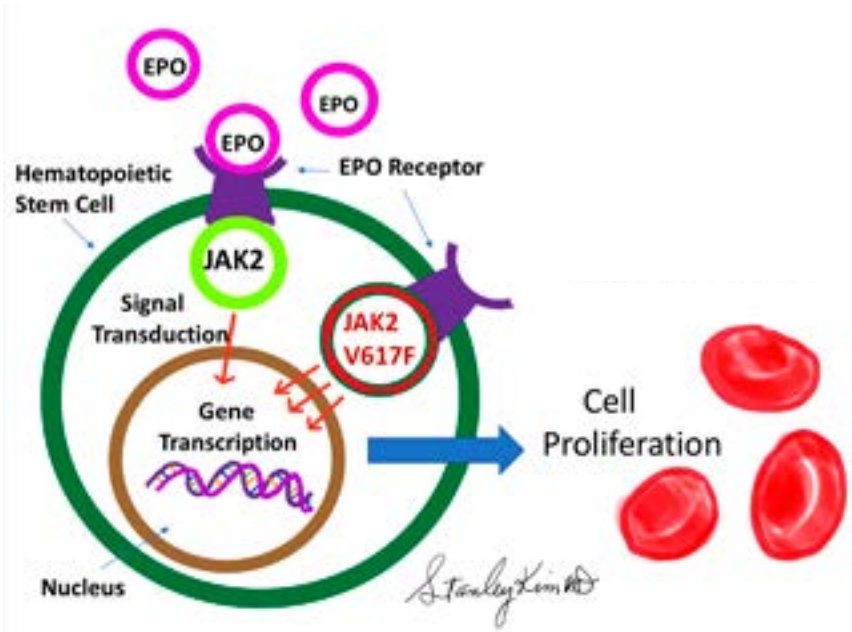
Physical examination showed BP 140/62, pulse oximetry in room air 97%, noticeably red face, no peripheral lymph node enlargement, normal heart and lung sounds, and no hepatosplenomegaly. The serum testosterone level was measured and was within normal limit at 654 ng/dL (normal; 250-827). The serum EPO level was also normal at 7.1 mIU/mL. Before investigating further for polycythemia, he was advised to stop the testosterone therapy and repeat CBC. The testosterone level decreased to 354 ng/dL as did the hemoglobin/hematocrit to 15.5 g/dL and 45%.

DISCUSSION

Clinicians may encounter polycythemia in the course of evaluating other clinical findings or incidentally on a routine laboratory test with complete blood count (CBC). The initial evaluation should enable the clinician to distinguish between relative polycythemia by plasma volume depletion from absolute polycythemia. Findings from the initial evaluation, together with the clinical scenario, should direct the subsequent evaluation to establish the underlying diagnosis.

FIGURE 1.

Normally, **JAK2** regulates erythropoiesis in response to the EPO. In Polycythemia Vera, the mutated **JAK2 V617F** can activate the signal transduction without EPO resulting in excessive erythropoiesis.



CAUSES AND CLINICAL MANIFESTATIONS OF POLYCYTHEMIA

Polycythemia Vera

Polycythemia Vera (PV) is a part of the myeloproliferative neoplasm (MPN). Other hematological conditions belonged to MPN include primary myelofibrosis, essential thrombocythemia and chronic myeloid leukemia.[2] It is caused by a mutation in a gene (JAK2) resulting in uncontrolled production of erythrocytes by the bone marrow. Normally, JAK2 regulates erythrocyte and platelet production in response to the EPO or TPO (thrombopoietin). But the mutated JAK2 (most commonly JAK2 V617F mutation) activates the signal transduction of hematopoietic stem cells in the absence of EPO or TPO. (Fig 1.). As a result, excessive erythrocytosis or thrombocytosis occurs without EPO or TPO stimulation.[2,3]

A somatic mutation (V617F) in the JAK2 gene is found in almost all PV patients. A study reported that 97% of PV patients are positive for the exon 14 V617F mutation, and the remaining 3% are positive for exon 12 V617F mutation, suggesting that either an exon 14 or 12 JAK2 mutation is present in virtually all patients with PV.[2,3] The JAK2 mutation is absent in normal subjects as well as those with secondary polycythemia. Thus, this mutation, when present, enables one to distinguish patients with PV from those with secondary polycythemia. However, the finding of the JAK2 V617F mutation is not specific for PV, since it is also present in a substantial proportion of patients with essential thrombocythemia (ET) as well as primary myelofibrosis.[6]

Symptoms of PV include headache, dizziness, generalized weakness, tinnitus, visual disturbances, chest pain, poor circulation of extremities, red face, and erythromelalgia. One of the interesting symptoms of PV is itching after warm bath occurring in 40% of patients due to high blood histamine level. The Histamine increases stomach acid secretion, which can cause peptic ulcer disease and stomach bleeding resulting in iron deficiency anemia. Splenomegaly is seen in 75% of patients and hepatomegaly in 30%.[7] Increased level of circulating RBCs increases the viscosity of the blood. This can be associated with high risk of thrombosis leading to stoke, acute coronary disease, deep vein thrombosis of extremities and pulmonary embolism.[8] High turnover rate of the blood cells results in high uric acid production, which can cause gout and uric acid kidney stones.[7]

Transformation to myelofibrosis (MF) and/or acute myeloid leukemia (AML) is a significant cause of mortality in PV and is likely largely related to disease duration. In large studies, progression to MF was reported in 9% to 21% of patients with PV, while evolution to AML has been documented in 3% to 10% of patients with PV. Risk factors for transformation include older age and leukocytosis.[9]

Secondary Polycythemia

When the body feels lack of O2 (hypoxia), the kidney produces erythropoietin (EPO) which is a hormone that promotes formation of RBCs by the bone marrow.[1] Conditions causing tissue hypoxia include chronic lung diseases (COPD), sleep apnea, cyanotic heart disease with right-to-left shunt, and living at high altitude. When tested with an oximetry, patients often have low O2 saturation.[5] However, secondary polycythemia due to chronic carbon monoxide poisoning do not show abnormally low O2 in the oximetry test. Chronic carbon monoxide poisoning is caused by heavy smoking, or malfunctioning gas heater or chimney.[10]

Certain tumors can produce the EPO, causing polycythemia: hepatocellular carcinoma, uterine fibroid tumor (leiomyoma), renal cell carcinoma, hemangioblastoma of the brain, meningioma, and pheochromocytoma.[11] Therefore, investigation for the underlying neoplasm should be considered when no other causes of secondary polycythemia are found. Increased EPO production can be the cause of secondary polycythemia after kidney transplantation or renal artery stenosis. The exact cause of polycythemia in those kidney problems is not known but appears to be related with decreased perfusion to the kidney. Testosterone increases the EPO level and decreases Hepcidin level, which result in erythrocytosis.[11]

Relative Polycythemia

Relative polycythemia is caused by decreased plasma volume and is often caused by loss of body fluids, such as through burns, dehydration, and stress.[2] Gaisbock's syndrome is an interesting relative polycythemia having a constellation of signs and symptoms: mild obesity; elevation of blood pressure (especially diastolic); decrease in plasma volume with relative increase in red cell count, hemoglobin, hematocrit, viscosity of blood, elevation of plasma proteins, serum cholesterol, triglycerides, uric acid, and plasma renin; and increased excretion of urinary sodium.[4]

Congenital Polycythemia

Primary familial and congenital polycythemia (PFCP) is a rare disease characterized by isolated erythrocytosis in an individual with a normal-sized spleen and absence of disorders causing secondary erythrocytosis. Patients have normal hemoglobin oxygen affinity measured as P50. The EPO level is low or in the lower normal range. It is inherited by autosomal dominant pattern.[7]

Altered oxygen affinity variant hemoglobins (Hb) are caused by mutations of the globin genes. Changes in Hb oxygen affinity shift the oxygen dissociation curve, which can be identified by abnormal P50 measurements of patient RBCs. Variants are categorized as either low oxygen affinity (high P50) or high oxygen affinity (low P50).[8]

DIAGNOSTIC APPROACH

Diagnostic approach of polycythemia starts at a through history and physical examination to determine the likely causes of high hemoglobin/hematocrit. Various symptoms and signs of primary and secondary polycythemia should kept in mind, including pulmonary symptoms, sleep apnea, smoking, itching after warm bath, dehydration, use of testosterone, the size of spleen, living at high altitudes, pulse oximetry result, etc. Measurement of the serum EPO level can distinguish secondary from primary polycythemia: if it is normal or high, secondary polycythemia is suspected, and if it is low, primary polycythemia (polycythemia vera). However, when patients with PV have underlying condition causing hypoxia such as COPD, the EPO level may not be low. The JAK2 mutation test is important. As the JAK2 mutation in exon 14 or exon 12 is seen in almost all patients of PV, it is difficult to diagnose PV without its positivity. The 2016 WHO criteria for the diagnosis of PV include the following:

Major criteria:

1. Increased hemoglobin level (>16.5 g/dL in men or >16.0 g/dL in women), hematocrit (>49 percent in men or >48 percent in women), or other evidence of increased red cell volume;
2. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size);
3. JAK2 V617F or JAK2 exon 12 mutation.

Minor criterion: Serum erythropoietin (EPO) level below the reference range for normal.

The diagnosis of PV requires the presence of all three major criteria or the presence of the first two major criteria

together with the minor criterion. These diagnostic criteria should be applied only to patients who have undergone the appropriate diagnostic evaluation to exclude secondary causes of polycythemia. The second major criterion (bone marrow biopsy) may not be required in cases with sustained absolute erythrocytosis (hemoglobin >18.5 g/dL or hematocrit >55.5 percent in men; hemoglobin >16.5 g/dL or hematocrit >49.5 percent in women) if the third major criterion and the minor criterion are present. Although, bone marrow biopsy may not be necessary to make a diagnosis of PV in certain cases, it is helpful to distinguish PV from other MPN such as essential thrombocythemia or myelofibrosis.[12]

Congenital polycythemia can be considered when polycythemia occurs in young children especially with a family history of polycythemia.

TREATMENT OF POLYCYTHEMIA

Polycythemia Vera

Low risk patients (younger age < 60 years; no history of venous or arterial thrombosis) just need therapeutic phlebotomy to keep Hct < 45%. All others are considered high risk and require cytoreductive therapy with phlebotomy as needed. Because the main goal of therapeutic phlebotomy is to induce iron deficiency to keep the hematocrit under the 45%, iron therapy is not recommended. However, in our experience of 30 years of medical practice, we have observed that patients with iron deficiency often complain of symptoms such as generalized weakness, headache, dizziness, difficulty in concentration, or restless leg syndrome. In those patients, cytoreductive therapy is preferred to reach the goal rather than inducing severe iron deficiency by multiple therapeutic phlebotomies. Practically, we prefer hydroxyurea for most patients with PV because of its quick onset of action and low risk of leukemogenesis,[9,13] but pegylated Interferon (IFN) alfa is the choice for younger patients (eg, <40 years) and those who might become pregnant.[14]

All patients need low dose aspirin unless the platelets > 1 mil/uL. Acquired von Willebrand Disease can develop in patients with PV, especially when the concomitant platelet count is very high,[15] in which case aspirin is contraindicated due to high risk of bleeding.

Severe pruritus and erythromelalgia are usually respond to low dose aspirin. For refractory pruritus, severe splenomegaly or post-PV myelofibrosis, ruxolitinib (JAKAFI®: JAK Inhibitor) is indicated. Alkylating agents such as Busulfan and radioactive phosphorus (^{32}P) have been used for elderly patients, but it can increase the incidence of acute leukemia.[13]

Anagrelide (Agrylin) is not preferred as a first line Tx because of high incidence of arterial thrombosis, major bleeding and myelofibrosis side-effects.[14]

Secondary Polycythemia

The management of secondary polycythemia should be focused on the treatment of underlying causes. Because secondary polycythemia is compensatory phenomenon to the hypoxic environment, patients may benefit from increased erythrocytosis. However, at certain point, too may RBCs result in increased blood viscosity, impairing tissue perfusion. Therefore, when patients develop symptoms of severe polycythemia, careful phlebotomy can relieve the symptoms and make patients feel better. In my practice, I phlebotomize patients with secondary polycythemia when the hemoglobin is above 20 g/dL, especially patients don't feel well with headache or generalized weakness.

AUTHOR DISCLOSURES:

No relevant financial affiliations or conflicts of interest.

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